Combined effects of fatigue and eccentric damage on muscle power

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Choi SJ, Widrick JJ. Combined effects of fatigue and eccentric damage on muscle power. J Appl Physiol 107: 1156–1164, 2009. First published August 6, 2009; doi:10.1152/japplphysiol.00403.2009.—Many physical activities can induce both transient and long-lasting muscle dysfunction. The separate and interactive effects of short-term fatigue and long-lasting contraction-induced damage were evaluated in an in vitro mouse soleus preparation (35°C) using the work loop technique. Repetitive fatiguing work loops reduced positive work (work produced by the muscle), increased negative work (work required to reextend the muscle), and reduced cyclical power (net work/time) immediately after treatment. These changes were readily reversible. The fatigue treatment had no long-term effects on optimal muscle length (Lₒ) and isometric force (Pₒ). High strain lengthening work loops, where the muscle contracted eccentrically, resulted in both immediate and long-lasting positive work, power, and Pₒ deficits as well as a shift in Lₒ to longer lengths. When the treatments were combined, i.e., fatigued muscles subjected to eccentric activity, the immediate power deficit exceeded the sum of the power deficits noted for the other two treatments. Much of this effect was due to an exaggerated rise in negative work. However, in the long term, power and Pₒ deficits and the shift in Lₒ were reduced compared with the damage-only treatment. These results show that 1) the immediate effects of combined fatigue and damage on cyclical power are synergistic, in large part because of a reduced ability of the muscle to relax; and 2) fatigued muscles are less susceptible to long-term contraction-induced dysfunction. Fatigue may protect against long-term damage by reducing the probability that sarcomeres are lengthened beyond myofilament overlap.

A better understanding of the interaction between muscle fatigue and damage would be expected to have important practical, clinical, and mechanistic implications. In this study, we used the work loop procedure to subject isolated mouse soleus muscles to repetitive cycles of shortening and lengthening. This approach mimics the repetitive, cyclical activity that muscles may undergo during in vivo locomotion (20, 23, 28). We varied the number, strain, and frequency of these cycles as well as the portion of the cycle when the muscle was stimulated to induce 1) short-term dysfunction, or fatigue; 2) longer-term dysfunction, referred to as damage; or 3) a combination of fatigue and damage. We evaluated the effects of these treatments on the recovery of cyclical power, a key determinant of skeletal muscle performance (23, 28). We also evaluated postrecovery isometric force (Pₒ) and optimal muscle length (Lₒ), two other indexes of muscle damage (1, 36, 37).

MATERIALS AND METHODS

Animals. Male ICR mice (Harlan, Indianapolis, IN, body weight: 40–50 g) were used in this study. All mice were housed under the same environmental conditions (12:12-h light-dark cycle at 22°C) with ad libitum access to a standard rodent diet and tap water. The use of these animals was approved by the Institutional Animal Care and Use Committee of Oregon State University.

Muscle preparation. On the day of an experiment, animals were anesthetized with pentobarbital sodium (40 mg/g body wt). Intact soleus muscles were dissected, and the animals were humanely euthanized. Silk sutures were used to attach the proximal tendon to the lever arm of a dual-mode muscle lever system (model 300B-RLR or model 305C, Aurora Scientific, Aurora, ON, Canada) and the distal tendon to a stable hook. We (40) have previously reported that the myosin heavy chain isoform distribution of the ICR soleus muscle is ~50% slow and ~50% fast.

The muscle was suspended vertically in bicarbonate buffer [containing (in mM) 137 NaCl, 5 KCl, 1.25 CaCl₂, 1.0 MgSO₄, 1.0 NaH₂PO₄, 24 NaHCO₃, 11 glucose, and 0.025 tubocurarine chloride] equilibrated with 95% O₂ and 5% CO₂. Buffer temperature was maintained at 35°C. Functional data were collected using a personal computer and a data acquisition board (model AT-MIO16E-10, Na-
tional Instruments, Austin, TX). Custom LabView programming (version 7.1, National Instruments) controlled the muscle stimulation (via a high-power biphasic current stimulator, model 701A, Aurora Scientific) and lever arm position while the force and length data were sampled (1,000 Hz). The data were recorded to disk and subsequently analyzed using programs written in LabView.

Experimental protocol. The experimental protocol consisted of the following steps: 1) determination of \( L_o \), 2) assessment of pretreatment \( P_o \) and cyclical power, 3) administration of the experimental treatment (10.2 s in duration), 4) evaluation of immediate posttreatment power (200 ms after the conclusion of the experimental treatment), 5) evaluation of cyclical power during recovery (every 3 min for 30 min), 6) assessment of postrecovery \( P_o \) (3 min after the final power recovery assessment), 7) reassessment of \( L_o \), and 8) measurement of final \( P_o \). In a subset of muscles, cyclical power was reevaluated 3 min after the conclusion of protocol step 8.

Assessment of \( L_o \). Tetani were induced with supramaximal 500-ms trains consisting of 200-μs square-wave pulses delivered at a frequency of 200 Hz. For protocol step 1, the muscle length was systematically altered every 3 min and force was reevaluated. The muscle length that produced maximal isometric force was defined as \( L_o \). This length was measured using a digital micrometer. At protocol step 7, muscles were shortened by 0.5 mm, and \( L_o \) was reassessed systematically. In all \( L_o \) assessments, the two muscles under study received the same number of contractions.

Assessment of \( P_o \). \( P_o \) was assessed using the stimulation parameters described above. \( P_o \) was normalized to the muscle’s physiological cross-sectional area. The latter variable was calculated from muscle mass, fiber length, and muscle density as previously described (53). Fiber length was estimated assuming a fiber length-to-\( L_o \) ratio of 0.71, a value previously determined for the ICR mouse soleus muscle in our laboratory (53).

Assessment of cyclical power. The ability of muscles to produce cyclical power was assessed using work loops. Muscles were subject to sinusoidal changes in length centered about their \( L_o \). Cycle amplitude and frequency were ±5% of fiber length and 5 Hz, respectively. These parameters are optimal for cyclical power output of the mouse soleus muscle at 35–37°C (4, 20). Power was optimized by initiating stimulation 15 ms before the muscle attained its maximum length (phase = 17.5%, where phase is defined as a percentage of the entire work loop cycle) and terminating stimulation 50 ms before the muscle reached its minimum length (phase = 50%). When power was assessed, muscles received three consecutive sinusoidal cycles. Force and length data were recorded and plotted to form a loop (see Fig. 1). Loop force was defined as the maximum force attained during the loop (measured from the \( L_o \) resting tension baseline). The work

Fig. 1. Optimal and lengthening work loop examples. A: optimal work loops. Sinusoidal changes in length were imposed upon the muscle (indicated by \( L \)). The cycle frequency was 5 Hz, and the cycle amplitude was ±5% of the fiber length [centered at optimal muscle length (\( L_o \)]. Muscle stimulation (indicated by \( S \)) was timed to optimize power (see METHODS for details). Force was recorded (indicated by \( F \)) and plotted against muscle length to form a work loop. In this example, the work loop obtained from the third cyclical contraction is shown. The arrow indicates the direction of loop. The length of 0.0 mm indicates \( L_o \). As shown by the shaded areas, negative work and positive work were calculated as the force × length integral during muscle lengthening and shortening, respectively. Net work was defined as positive work minus negative work, i.e., the area enclosed by the work loop. Net work per unit time defined cyclical power. The time scale is identical for \( L \), \( S \), and \( F \) records. The force scale pertains to both the \( F \) record and work loops. B: lengthening work loops. Sinusoidal changes in length were imposed upon the muscle (indicated by \( L \)) at a frequency of 2 Hz and an amplitude of ±25% of the fiber length (centered at \( L_o \)). Muscles stimulation (indicated by \( S \)) was timed to maximize force during lengthening (see METHODS for details). Force was recorded (indicated by \( F \)) and plotted against muscle length to form a work loop. In this example, only the initial 3 of 10 cyclical contractions are shown, and the work loop obtained from first cyclical contraction is shown. The arrow indicates the direction of loop. The length of 0.0 mm indicates \( L_o \). Negative work, positive work, net work, and power were calculated as described in A. The time scale is identical for \( L \), \( S \), and \( F \) records. The force scale pertains to both the \( F \) record and work loops. Note that the time scale and amplitude of the \( L \), \( F \), and work loop records differ from A. For a direct comparison of optimal and lengthening work loops, see Fig. 2.
produced by the muscle (shortening or positive work) and the work absorbed by the muscle (lengthening or negative work) were defined as the force by length integrals during muscle shortening and muscle lengthening, respectively. Net work was calculated as work produced minus work absorbed. Cyclical power was defined as net work per unit time. We expressed work and power relative to muscle mass to be consistent with the animal locomotion literature (4, 20). Because muscle density is only slightly greater than 1.00 (1.06 mg/mm³), values expressed in this manner are within a few percent of work or power per unit muscle volume.

**Experimental treatments.** Both soleus muscles were studied from each mouse. Each soleus muscle was assigned to one of four treatments: control (C), fatigue (F), damage (D), or fatigue and damage (FD). Assignment was arranged so that two consecutively studied muscles completed one replicate of all four experimental treatments.

All of the experimental treatments consisted of a 5.0-s stage 1 and a 5.0-s stage 2, separated by 200 ms, for a total treatment time of 10.2 s. For the C treatment, muscles were not administrated any length change or stimulation during this time period. The F, D, and FD treatments are shown in Fig. 2. For the F treatment, muscles were administrated 25 cyclical contractions using the same parameters and stimulation timing as used for the assessment of optimal power. The first cyclical contraction coincided with the initiation of the treatment period. Thus, work loops occurred during the initial 5.0 s of the treatment period with the muscle quiescent during the remaining 5.2 s.

For the D treatment, muscles were administered 10 consecutive cyclical contractions at an amplitude of ±25% of fiber length and a cycle frequency of 2 Hz. To activate the muscle during the lengthening portion of the cycle, stimulation was initiated 15 ms before the cycle frequency of 2 Hz. Stimulation was timed to phase the muscle attained its shortest length (phase initiation of the cycle). Thus, the fatigue cycles occurred between the treatment time points of 0.0 and 5.0 s and the damaging cycles between 5.2 and 10.2 s, identical to the timing of the F-only and D-only treatments, respectively.

**Statistical analysis.** As has been reported by others (4, 20), we found that power was maximized on either the second or third work loop, with a <1% difference between these loops. Therefore, data from the third loop were used for statistical analysis.

All data are presented as means ± SE. Variables were analyzed with one-way ANOVA (main effect of treatment) or two-way repeated-measures ANOVA (main effects of treatment and time, treatment × time interaction). In the event of a significant F ratio, the Holm-Sidak post hoc procedure was used to identify differences between specific means. The type I error rate was <0.05. All analyses were performed using SigmaPlot 11.0 (Systat Software, San Jose, CA).

**RESULTS**

**Characteristics of the muscles before treatment.** Observed mean values for $P_o$ (254 ± 9 kN/m², $n = 28$) and cyclical power (35.5 ± 1.4 W/kg, $n = 28$) were in good agreement with literature values for the mouse soleus muscle at 35–37°C [212–287 kN/m² (Refs. 3, 4, 20, and 48) and 33–34 W/kg (Refs. 4 and 20)]. There were no between-group differences in soleus mass, $L_o$, $P_o$, or any work loop parameters before treatment (Table 1). The maximal force attained during the pretreatment cyclical contractions, or loop force, averaged $46 ± 1\%$ ($n = 28$) of peak $P_o$ (no differences between treatments).

**Responses to the fatigue protocol (F and FD treatments).** Because they had received no prior treatment, muscles in the F and FD treatments responded similarly to the fatigue protocol. On the 25th (final) cycle of the protocol, loop force was reduced by 16% (Fig. 3A) and power was reduced by 48% (Fig. 3B) compared with the peak values measured on the 3rd cycle. As shown in Fig. 3B, the reduction in power was substantially greater than the reduction in loop force.
1.87-fold greater than pretreatment Po (Table 1 and Fig. 4; on average, 3.95-fold greater than the pretreatment loop force and force attained on the initial lengthening cycle of the D treatment was, for clarity, only expressed as a percentage of the peak loop force attained on the third cycle. For the FD treatment, loop force declined 25% across 10 successive lengthening cycles (Fig. 4A). The total work absorbed by the muscle averaged 1,347 ± 49 J/kg (Fig. 4B). During the FD treatment, muscles showed similar rates of absolute force decline and work absorption as the D treatment (Fig. 4, A and B; no significant interactions). However, because of the prior fatigue protocol, force on the initial lengthening cycle averaged 19% less for the FD treatment. Thus, the FD muscle experienced less relative decline in force during the damage protocol (Fig. 4B), and the total work absorbed by the muscle was 11% less (Fig. 4B).

Values are means ± SE; n = 7 muscles/treatment. All work loop data are from the third cycle of the pretreatment assessment. There were no between-treatment differences for any variable (P > 0.05).

because the change in power reflected a reduction in positive work (17% reduction from peak) coupled with an increase in negative work (50% increase above minimum).

Responses to the damage protocol (D and FD treatments). Loop force attained on the initial lengthening cycle of the D treatment was, on average, 3.95-fold greater than the pretreatment loop force and 1.87-fold greater than pretreatment P0 (Table 1 and Fig. 4A). For the D treatment, loop force declined 25% across 10 successive lengthening cycles (Fig. 4A). The total work absorbed by the muscle averaged 1,347 ± 49 J/kg (Fig. 4B). During the FD treatment, muscles showed similar rates of absolute force decline and work absorption as the D treatment (Fig. 4, A and B; no significant interactions). However, because of the prior fatigue protocol, force on the initial lengthening cycle averaged 19% less for the FD treatment. Thus, the FD muscle experienced less relative decline in force during the damage protocol (Fig. 4B), and the total work absorbed by the muscle was 11% less (Fig. 4B).

Immediate posttreatment power. Cyclical power measured immediately after the C treatment averaged 100 ± 0% (range: 98.5–101.2%) of the pretreatment value (Figs. 5 and 6A). The F, D, and FD treatments all showed significant reductions in cyclical power compared with the C treatment. These changes are evident in the representative experiments shown in Fig. 5 as reductions in the area enclosed by the work loop, although the extent that power declined differed greatly across treatments. The average smallest reduction was observed after the F treatment, where power was 27% lower than the pretreatment value (Fig. 6A). This decline was attributed to a reduction in positive work (Fig. 6B) coupled with an increase in negative work (Fig. 6C). The reduction in positive work was proportional to a loss in the ability of the muscle to produce force (Fig. 6D).

Power was reduced 34% by the D treatment, which was a greater decline than noted after the F treatment (Fig. 6A). However, in contrast to the F treatment, the power deficit after the D treatment was due entirely to a reduction in positive work (Fig. 6, B and C). In fact,
negative work fell after the D treatment, a change that would tend to increase power output.

The greatest power deficit was observed after the FD treatment, where power was 84% lower than the pretreatment value (Fig. 6A). The representative FD experiment shown in Fig. 5 demonstrates a greatly impaired ability of the muscle to produce force and to fully relax at the conclusion of the posttreatment stimulation, resulting in a reduction in work during shortening and an increase in work during the lengthening portion of the cycle. On average, the FD treatment induced the greatest reduction in positive work coupled with the greatest increase in negative work compared with all other treatments (Fig. 6, B and C).

Recovery power and Po. As shown by the solid bars in Fig. 7A, there were no long-term changes in Po for the C and F treatments. However, the D treatment resulted in a long-term Po deficit of 26%. A Po deficit also existed after the FD treatment, but its magnitude was half that observed for the D-only treatment.

Reassessment of Lo and Po. As shown by the open bars in Fig. 7A, the C and F treatments had no effect on Lo and, consequently, no effect on the final Po evaluation (shaded bars in Fig. 7A). In contrast, Lo was 9.6 ± 0.7% longer after the D treatment. When force was evaluated at this new length, the Po deficit was reduced from 26% to 18%. The FD treatment also showed a significant increase in Lo after recovery, but the magnitude of this increase was roughly half (4.3 ± 0.5%) of the increase noted for the D treatment. When Po was reevaluated at this new Lo, the Po deficit was reduced from 13% to 9%.

Reassessment of cyclical power. Figure 7B shows mean cyclical power measured in a subset of muscles after the reassessment of Lo. There were no changes in cyclical power from the original Lo to the final Lo for the C or F treatments. However, cyclical power decreased for the D and FD treatments at the final, longer Lo. This reduction in power at the reassessed Lo, despite an increase in force at this muscle length, was due mainly to an elevation in negative work.

Fig. 5. Examples of pretreatment, posttreatment, and recovery work loops. Each row represents an individual experiment. Force was recorded during three cyclical contractions, performed as in Fig. 1, and a work loop was calculated using force and length data from the third cycle. Each muscle was then subjected to a different experimental treatment: no treatment [control (C)], F treatment, D treatment, or FD treatment. Immediate posttreatment force and work loops (illustrated by the thin lines) and recovery force and work loops (recorded 30 min later and indicated by the thick lines) were then obtained using the same parameters used for the pretreatment measurements. Pretreatment cyclical power was 45.7, 43.3, 45.1, and 40.3 W/kg for the C, F, D, and FD treatments, respectively. For the C treatment, posttreatment and recovery power were 99% and 99%, respectively, of the pretreatment value. Corresponding values for the F, D, and FD treatments were 78% and 101%, 59% and 66%, and 18% and 99%, respectively. Force, time, and length scales are identical for all treatments shown. All work loops proceed counterclockwise.
DISCUSSION

Definitions. Both muscle fatigue and muscle damage can be characterized by a loss in muscle function (13, 37). This does not imply that the mechanisms responsible for these functional changes are similar. Indeed, the mechanisms differ because fatigue and damage can be distinguished by their time course of recovery: fatigue is a relatively transient depression in function, whereas damage requires days to weeks for full recovery (13, 37). We used repetitive work loops, conducted using parameters that optimized pretreatment power output, to induce a transient and reversible loss in cyclical power (F treatment), which we define as fatigue. Within the 30 min postrecovery limitation imposed by this study, a long-term functional depression, which we define as damage, were induced by a protocol in which the muscle performed lengthening or eccentric contractile activity during larger magnitude work loops (D treatment). While these descriptive definitions may have limitations (for instance, they are inconsistent with a long-lasting dysfunction termed low-frequency fatigue (7, 22)), they are generally accepted and have been used in this report.

The work loop model. The work loop procedure was developed to model the repetitive, cyclical muscular activity that is characteristic of aquatic, airborne, and terrestrial locomotion (23, 28). Because movement requires a net positive work output by skeletal muscles, cyclical power is a key determinant of animal locomotion. The magnitude of a muscle’s cyclical power is dependent on its length-tension relationship, its force-velocity relationship, and its rate of activation and relaxation (23, 28). Damaging lengthening contractions have long-term effects on all of these properties (32, 48, 53), whereas fatigue has transient effects on the force-velocity relationship and muscle activation/relaxation (12, 15, 44, 51). We therefore reasoned that work loops would provide a comprehensive approach for assessing the separate and interactive effects of fatigue and damage on muscle performance.

We attempted to study work loops under physiologically relevant conditions. The cycle amplitude and cycle frequency used for optimal power determination fell well within the range of soleus strain amplitudes and stride frequencies calculated during normal mouse gait (20). The strain magnitude during the lengthening contractions also fell within the physiological range (8). However, the sinusoidal changes in length used here are probably a simplification of the more complex patterns of shortening and lengthening that muscles may undergo in vivo (28). Thus, the preparation studied here should be considered a generalized model of muscle function, but not necessarily representative of any specific muscle.

One limitation of our approach is the possibility that the D treatment induced some fatigue as the muscle was being damaged. Lengthening contractions result in less perturbation of intracellular high-energy phosphate homeostasis compared with shortening contractions (38) and are therefore less likely to induce fatigue. While we tried to take advantage of this in the design of our experiment, there is a small increase in power over the initial minutes of recovery from the D treatment. This suggests that some fatigue may have occurred during the D portion of the D and FD treatments. However, the recovery after the D treatment was clearly limited and substantially different from the complete recovery of power observed 6 min after the completion of the F treatment. Thus, for the D treatment, any fatigue effect was considerably less than the amount of damage that occurred. For the FD treatment, any fatigue produced during the D portion would mean that slightly more fatigue occurred in this treatment than during the F-only
Lengthening contractions (D treatment) resulted in an immediate and persistent power loss. This was attributed to a reduction in positive work that was offset, to some extent, by a reduction in negative work. Long-term reductions in positive work, negative work, and power have been previously reported for muscles subjected to lengthening contractions and work loops (6, 42). The D treatment also induced a long-term reduction in \( P_0 \) and a shift in \( L_o \) toward longer lengths. This long-term reduction in \( P_0 \) may represent deficits at the level of excitation-contraction coupling, the thin filament, or the cross bridge (5, 19, 46). The shift in \( L_o \) toward longer lengths reflects an increase in muscle compliance due to the existence of disrupted sarcomeres (6, 32, 46).

The novel contributions of this work pertain to FD treatment. Fatigued muscles subjected to high strain lengthening contractions (FD treatment) showed greater immediate reductions in power than either the F or D treatments. However, when allowed to recover, FD-treated muscles showed greater restoration of power, a lesser \( P_0 \) deficit, and a shorter shift in \( L_o \) compared with the D-only treatment. Thus, the main conclusions of this investigation are that prior fatigue 1) exacerbated the immediate power loss but 2) reduced the long-term power, force, and \( L_o \) changes associated with lengthening contractions.

**Immediate effects.** The mechanism responsible for the loss of cyclical power immediately after the FD treatment appears to be related to an exacerbated increase in negative work as muscles failed to completely relax as they were extended in preparation for another cycle of shortening. While the mechanism responsible for this effect in the FD treatment cannot be determined from the present study, it would have to have the following characteristics: 1) present only when lengthening is combined with fatigue and 2) readily reversible in a time course roughly similar to the restoration of positive work. Stretch-activated channels that are activated during lengthening contractions (29) and allow \( Ca^{2+} \) influx into the cell (39) may be a mechanism underlying these observations. A nonfatigued fiber subjected to lengthening contractions may be able to adequately buffer \( Ca^{2+} \) entering through these channels. A fatigued fiber, where sarcoplasmic reticulum \( Ca^{2+} \) uptake may already be compromised (52), may be unable to buffer any additional \( Ca^{2+} \) influx that occurs as a result of lengthening contractions. This inability to buffer \( Ca^{2+} \) might then impair relaxation. Additional work will be required to test this hypothesis.

**Long-term effects.** The long-term effect of fatigue was to reduce dysfunction due to lengthening contractions. This result, obtained on a mixed-fiber composition, oxidative muscle, is in agreement with the results of McNally and Faulkner (30), who studied the glycolytic, fast extensor digitorum longus muscle. Taken together, these two studies suggest that the interactive effect of fatigue and damage is not confined to muscles of a particular fiber type or metabolic profile. Nosaka and Clarkson (34) reported that prior fatigue reduced indexes of muscle damage and soreness in the elbow flexors of human volunteers. Our results suggest that the observations of Nosaka and Clarkson can be explained by processes within the muscle per se.

In contrast to the present work, Morgan et al. (32) concluded that fatigue had no effect on long-term damage from eccentric contractions in that it did not prevent a fall in \( P_0 \) or a shift in \( L_o \). In the Morgan et al. study (32), different portions of the cat muscle were used, and the authors suggested that the differences in results may be due to the different muscle types used.

The absence of any functional change during the C treatment is in agreement with the results of McNally and Faulkner (30), who studied the glycolytic, fast extensor digitorum longus muscle. Taken together, these two studies suggest that the interactive effect of fatigue and damage is not confined to muscles of a particular fiber type or metabolic profile. Nosaka and Clarkson (34) reported that prior fatigue reduced indexes of muscle damage and soreness in the elbow flexors of human volunteers. Our results suggest that the observations of Nosaka and Clarkson can be explained by processes within the muscle per se.
gastrocnemius muscle were subjected to 10 eccentric contractions to induce damage, 200 concentric contractions to induce fatigue, or 200 contractions followed by 10 eccentric contractions. Because the eccentric contractions were separated by 30 s of rest, it required almost 5 min to subject a previously fatigued muscle to all 10 eccentric contractions. It is possible that the muscle could have recovered from some or all of the effects of the fatiguing contractions while awaiting the entire eccentric treatment. This might have blunted any effects of fatigue and explain why their conclusions differ from ours.

An important question is the mechanisms by which prior fatigue reduced subsequent damage from lengthening contractions. One possibility is that by reducing force, fatigue lowers the stress experienced by the muscle as it is actively stretched. Maximum force during lengthening is clearly associated with the extent of eccentric-induced muscle damage (30, 47). However, this strong association may simply be due to covariation of force with another factor, or factors, that are truly causative. Talbot and Morgan (45) studied toad muscles with very low passive force characteristics to vary sarcomere length without inducing large changes in total force. They reported that the change in sarcomere length, but not force, was significantly correlated with the posteccentric isometric force deficit and increase in optimal length. Likewise, Lieber and Friden (25) found that mammalian muscles lengthened at the onset of stimulation showed force deficits similar to muscles allowed to attain peak force before lengthening, even though the maximum force attained in the latter case was 33% greater. Because maximum attained force does not appear to be a causative factor in lengthening-induced muscle damage, it seems unlikely that the force protocol studied here conferred its protective effects via a reduction in force per se.

Several experimental approaches have suggested that damage may be causally linked to strain magnitude and sarcomere length heterogeneity (25, 26, 35, 45). We propose that the fatigue-induced long-term reduction in damage observed here can be interpreted in terms of sarcomere heterogeneity, as put forward by Morgan and colleagues (31, 37) in their popping sarcomere hypothesis of muscle damage. The popping sarcomere hypothesis states that much of the length change during stretching of an active muscle is taken up by a relatively small number of sarcomeres. When one of these sarcomeres is extended onto the descending limb of its length-active tension relationship, it will continue to lengthen until its total tension is equal to the tension produced by in series sarcomeres (which remain on the plateau of their length-tension relationship). If this sarcomere is overextended beyond thin and thick myofilament overlap, myofilaments may fail to reinterdigitate when the muscle is returned to its original length, rendering the sarcomere nonfunctional. The mechanical strain resulting from the continued overextension of this now-compliant sarcomere may then be propagated longitudinally and radially to neighboring sarcomeres, causing the disruption of cross bridges, t-tubules, the sarcoplasmic reticulum, and sarcolemma (1).

In a short communication, Morgan and Proske (33) proposed that sarcomere popping may be reduced or eliminated under conditions of partial activation because a sarcomere does not need to be extended as far along its total tension curve before its force is equal to the (reduced) active force of in-series sarcomeres. Under these conditions, there is a reduced likelihood that the thin and thick myofilaments will be extended beyond overlap and a reduced likelihood of sarcomere popping. We propose that fatigue, by reducing the force of the sarcomeres that remain on the plateau of the length-tension relationship, causes similar behavior.

In this model, fatigue would reduce long-term dysfunction by decreasing the likelihood of sarcomere overextension beyond thin and thick filament overlap. In the nonfatigued state, the length at which the total tension of an overextended sarcomere equilibrates (with the tension of the sarcomeres remaining on the plateau of the length-tension relationship) is only slightly longer than the length at which thin and thick filaments no longer overlap (see Fig. 1 of Ref. 32 and Fig. 7 of Ref. 41). Thus, even a small decrease in the active tension of in-series sarcomeres (a decrease in the plateau of the length-tension relationship) has the potential to substantially reduce sarcomere popping. This is consistent with the present results in which a relatively mild fatigue protocol prevented much of the long-term loss in power and increase in optimal length attributed to lengthening contractions. This model also explains why force deficits were reduced in skinned fibers that were only partially Ca\(^{2+}\) activated during lengthening (27) and why postlengthening force deficits were greater in fibers in which force had been potentiated by phosphorylation of the regulatory light chain (10).

There may be other factors contributing to our results. The optimal length for twitches occurs at a longer sarcomere length than for tetanic contractions (11). If fatigue causes a similar shift to a longer \(L_o\) due to a reduction in activation, then the relative number of sarcomeres extended onto the descending limb would be reduced. Repetitive contractions may also alter the passive tension-sarcomere length relationship. The stiffness of the titin filament, which confers passive tension to the sarcomere (17), has recently been shown to be increased by elevations in intracellular Ca\(^{2+}\) and by repetitive contractions (9, 24). A shift in the length-passive tension relationship to the left (i.e., toward shorter sarcomere lengths) would be expected to reduce the overextension of sarcomeres and lower the probability of sarcomere popping. There is a rise in intracellular Ca\(^{2+}\) in mildly fatigued muscle (50), and it may be important to test whether this is sufficient to stiffen titin and stabilize sarcomeres extended onto the descending limb of their length-tension relationship.

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